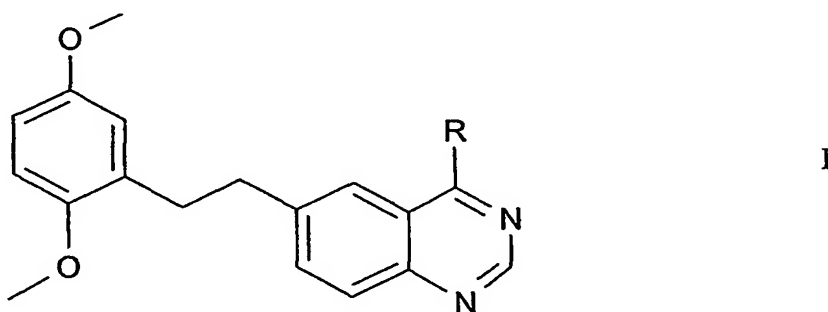


Pharmaceutical compositions

The invention relates to topical pharmaceutical compositions in the form of an emulsion comprising a lavendustin derivative.

It particularly concerns **topical pharmaceutical compositions** comprising a **lavendustin derivative of formula I**



wherein R is methyl, methoxy or ethyl, or a pharmaceutically acceptable salt thereof, and an **emollient**, hereinafter briefly named "**the compositions of the invention**".

The compounds of formula I are known, e.g. as Example 6 (R = ethyl, hereinafter **compound A**), Example 16 (R = methoxy, hereinafter **compound B**), and Example 17 (R = methyl, hereinafter **compound C**) in USP 5'990'116, the contents of which is incorporated herein by reference.

Preferred is 6-[2-(2,5-dimethoxyphenyl)ethyl]-4-ethyl-quinazoline (compound A).

These compounds are useful in the topical treatment of hyperproliferative disorders such as actinic keratosis, anogenital warts and seborrheic keratosis, and skin cancer. Hyperproliferative skin disorders are often accompanied by a hyperkeratosis. In particular, actinic keratosis is a skin disease with horny and dry skin lesions.

Treatment of hyperproliferative disorders can include destructive methods (cryotherapy, electro-desiccation and curettage, excisional therapy) and topical chemotherapy. Destructive methods and surgery may cause pain, blistering, scars and pigment changes and therefore, especially for patients with multiple lesions, topical chemotherapy is preferred.

Little is known about the mechanism of action of lavendustins, e.g. of formula I as defined above, but like other antiproliferative agents they may cause skin irritation. For example, a composition of 0.5 % w/w of lavendustin of formula (I) in ethanol/water showed severe skin irritation potential in an in vitro human epidermis model.

It has now been found that compositions comprising lavendustin or a lavendustin derivative, such as those of formula I as defined above and an emollient may be formulated into compositions of good physico-chemical stability, having good penetration and good tolerability and allowing application on skin, e.g. face, and mucous membranes. They avoid high local concentration of the lavendustin in the skin and mucous membrane and therefore are well tolerated.

Accordingly the invention provides in one aspect, a **topical pharmaceutical composition comprising lavendustin or a lavendustin derivative**, e.g. of formula I as defined above or a pharmaceutically acceptable salt thereof, **and an emollient**.

Suitable **emollients** may be selected from e.g.:

- i) **liquid fatty alcohols**, saturated and/or unsaturated, branched and/or unbranched, having e.g. a C₈ to C₂₄ chain. Preferred is **oleyl alcohol**, e.g. as known and commercially available under the trademark **HD Eutanol^R** from e.g. Henkel, Germany;
- ii) **liquid waxes**, e.g. natural, synthetic, semisynthetic or emulsifying waxes, preferably **isopropyl myristate**, e.g. as known and commercially available from Henkel, Germany; **oleyl erucate**, e.g. as known and commercially available under the trademark **Cetiol^R J600** from e.g. Henkel, Germany; **diisopropyl adipate**, e.g. as known and commercially available under the trademark **Isopat[®] 1794** from e.g. Dargoco, Germany; and/or **oleyl oleate**, e.g. as known and commercially available under the trademark **Cetiol^R** from e.g. Henkel, Germany;
- iii) **di- and triglycerides**, having e.g. C₈ to C₂₄ fatty acids, e.g. a **medium chain fatty acid triglyceride**, e.g. **Miglyol^R 812**. Miglyol^R 812 is a fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight of about 520 daltons. Fatty acid composition: C₆ max. about 3 %, C₈ about 50 to 65 %, C₁₀ about 30 to 45 %, C₁₂ max. 5 %; acid value about 0.1; saponification value about 330 to 345; iodine value max. 1. Miglyol^R 812 is commercially available from e.g. Hüls Chemie AG, Germany;

- iv) **propylene glycol mono- and di-fatty acid esters** such as propylene glycol caprylate, commercially available under the trademark Miglyol^R 840 (H.P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete 2 [2002] 5th Ed., Editio Cantor Verlag Aulendorf, p. 1130-1131), propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, and propylene glycol stearate;
- v) **petrolatum**, e.g. **white petrolatum**, e.g. as known and commercially available from e.g. Mineral Chemie AG, Germany; and
- vi) mixtures of any of components i) to v).

The lavendustin or lavendustin derivative is present in the compositions of the invention in an amount of from about 0.01 to about 10 %, e.g. from about 0.05 to about 3 %, e.g. from about 0.1 to about 2 %, e.g. from about 0.2 to about 1 %, e.g. about 0.2 or about 0.8 % by weight based on the total weight of the composition.

The emollient may be present in an amount of from about 5 to about 40 %, preferably from about 5 to about 30 % by weight based on the total weight of the composition.

The compositions of the invention are preferably in form of emulsions, more preferably in the form of oil-in-water emulsions. Accordingly, the invention further provides **topical pharmaceutical compositions in form of an emulsion**, e.g. in form of an oil-in-water emulsion, **comprising lavendustin or a lavendustin derivative**, e.g. of formula I, or a pharmaceutically acceptable salt thereof, **and an emollient**.

Preferably, the lavendustin or lavendustin derivative, e.g. of formula I, or a pharmaceutically acceptable salt thereof is dissolved in the lipophilic components, such as the emollient(s), and is released from the formulation in a uniform and sustained manner thereby avoiding high local concentrations, i.e. concentrations which could cause irritation, of the lavendustin derivative in the skin or mucous membrane.

In another aspect, the invention thus provides **topical pharmaceutical compositions comprising lavendustin or a lavendustin derivative**, e.g. of formula (I), or a pharmaceutically acceptable salt thereof **which avoid high local concentration** of the lavendustin in the skin or mucous membrane and therefore are well tolerated.

The compositions of the invention may further comprise **hydrophilic components** such as **propylene glycol**; hexylene glycol; liquid polyethylene glycol such as PEG 200, 300, 400 or 600; and/or **glycerol (glycerine)**. The hydrophilic components may be present in amounts of from about 1 up to about 20 %, e.g. from about 1 to about 5 % by weight based on the total weight of the composition.

The compositions of the invention may further comprise **water**, e.g. **purified water**. Water may be present in amounts of from about 20 up to about 90, e.g. from about 35 to about 80 % by weight based on the total weight of the composition.

The compositions of the invention may further comprise **emulsifiers**. Such emulsifiers are described in standard texts such as Fiedler, loc. cit. ; and A.H. Kibbe Handbook of Pharmaceutical Excipients (2000), a joint publication of Pharmaceutical Press, London (UK) and American Pharmaceutical Association, Washington (US). Examples of suitable emulsifiers include:

- i) **sorbitan fatty acid esters**, e.g. sorbitan mono C₁₂₋₁₈ fatty acid esters; sorbitan sesqui C₁₂₋₁₈ fatty acid esters; and sorbitan tri C₁₂₋₁₈ fatty acid esters, as known and commercially available under the trademark Span® or Arlacel®. Particularly preferred are the products
 - Span^R 20, a sorbitan monolaurate, having a D²⁵ of about 1, a HLB of about 8.6, and a viscosity of about 3900 to 4900 mPa's;
 - Arlacel^R 83, a sorbitan monosesquioleate, having a D²⁵ of about 1, a HLB of about 3.7, and a viscosity of about 1500 mPa's; and
 - Span^R 60, a sorbitan monostearate, having a HLB of about 4.7, and an acid value of about 5 to 10 (Fiedler, loc. cit., p. 1571-1572; Handbook of Pharmaceutical Excipients, loc. cit., page 511);
- ii) **polyoxyethylene-sorbitan-fatty acid esters**, for example mono- and tri-lauryl, palmityl, stearyl and oleyl esters of the type also called polysorbates, known and commercially available under the trademark Tween® (Fiedler, loc. cit. p.1754-1757; Handbook of Pharmaceutical Excipients, loc. cit., p. 416), including the products Tween^R
 - 20 [polyoxyethylene(20)sorbitanmonolaurate];
 - 21 [polyoxyethylene(4)sorbitanmonolaurate];

- 40 [polyoxyethylene(20)sorbitanmonopalmitate];
- 60 [polyoxyethylene(20)sorbitanmonostearate];
- 65 [polyoxyethylene(20)sorbitantristearate];
- 80 [polyoxyethylene(20)sorbitanmonooleate];
- 81 [polyoxyethylene(5)sorbitanmonooleate];
- 85 [polyoxyethylene(20)sorbitantrioleate].

Especially preferred products of this class are Tween^R 20 and Tween^R 60;

- iii) **salts of fatty alcohol sulfates** such as sodium lauryl sulfate and **sodium cetylstearyl sulfate**, preferably sodium cetylstearyl sulfate as known and commercially available under the trademark **Lanette^R E** (Fiedler, loc. cit., p. 1007-1008) from Henkel, Germany;
- iv) **polyoxyethylene alkyl ethers**, e.g. polyoxyethylene glycol ethers of C₁₂ to C₁₈ alcohols, e.g. polyoxyethylene cetyl ether or polyoxyethylene oleyl ether, or polyoxyethylene stearyl ether, as known and commercially available under the trademark Brij^R (Fiedler, loc. cit., p. 325-327; Handbook of Pharmaceutical Excipients, loc. cit., page 407);
- v) **polyoxyethylene fatty acid esters**, for example polyoxyethylene stearic acid esters of the type known and commercially available under the trademark Myrj^R (Fiedler, loc. cit., p. 1166-1167; Handbook of Pharmaceutical Excipients, loc. cit., page 420). An especially preferred product of this class is e.g. Myrj^R 52, a polyoxyethylene 40 stearate having D²⁵ of about 1.1, a melting point of about 40 to 44°C, a HLB value of about 16.9, an acid value of about 0 to 1 and a saponification number of about 25 to 35;
- vi) **polyoxyethylene-polyoxypropylene copolymers and block co-polymers** such as those known and commercially available under the trade names Pluronic^R, Emkalyx^R, and Poloxamer^R (Fiedler, loc. cit., p. 1330-1332, 1334; Handbook of Pharmaceutical Excipients, loc. cit., page 386) and in particular Poloxamer^R 188 and Pluronic^R F68 having a D²⁵ of about 1.1, a melting point of about 40 to 44°C, and a HLB value of about 16.9;
- vii) **esters of polyethylene-glycol glycerol ethers which have at least one free hydroxyl group and aliphatic C₆-C₂₂ carboxylic acids**. Examples include glycerine mono stearate (PEG-20);
- viii) **reaction products of a natural or hydrogenated castor oil and ethylene oxide**. The polyethyleneglycol hydrogenated castor oils are available under the trademark Cremophor^R (Fiedler, loc. cit., p. 472-475). Particularly suitable are:

- Cremophor^R RH 40, having a saponification value of about 50 to 60, an acid value of less than about 1, a water content (Fischer) of less than about 2 %, a n_D^{60} of about 1.453 to 1.457 and a HLB of about 14 to 16;
- Cremophor^R RH 60, having a saponification value of about 40 to 50, an acid value of less than about 1, an iodine value of less than about 1, a water content (Fischer) of about 4.5 to 5.5%, a n_D^{25} of about 1.453 to 1.457 and a HLB of about 15 to 17; and
- Cremophor^R EL, having a molecular weight (by steam osmometry) of about 1630, a saponification value of about 65 to 70, an acid value of about 2, an iodine value of about 28 to 32 and a n_D^{25} of about 1.471.

Also suitable are various tensides available under the trademark Nikkol^R (Fiedler, loc. cit., p. 1210-1211), Emulgin^R (Fiedler, loc. cit., p. 637), Mapeg^R (Fiedler, loc. cit., p. 1086) and Incrocas^R (Fiedler, loc. cit., p. 908);

- ix) **polyethylene glyceride** as commercially available under the trademark Labrafil^R (Fiedler, loc. cit., p. 880), particularly Labrafil^R M2130 CS;
- x) **glycerine sorbitan fatty acid esters** as commercially available under the trademark Arlancel^R 481, having a molecular weight of about 630, and a HLB value of about 4.5 (Fiedler, loc. cit., p. 247-249); and
- xi) mixtures of any of components i) to x).

It is to be appreciated that emulsifiers may be complex mixtures containing side products or unreacted starting products involved in the preparation thereof, e.g. emulsifiers made by polyoxyethylation may contain another side product, e.g. polyethylene glycol.

When the composition is a water-in-oil emulsion, the emulsifier selected preferably has a HLB value of about 10 to 15. When the emulsion is an oil-in-water emulsion, the emulsifier selected preferably has a HLB value of about 4 to 8. A combination of emulsifiers having different HLB values may be used to achieve a desired HLB value. Preferably the emulsifiers are present in an amount of from about 1 to about 30 % by weight based on the total weight of the composition, more preferably from about 10 to about 25 %.

Preferably, the compositions of the invention are in form of a **cream, a lotion or an emulsion gel**, especially a cream.

If desired, the compositions of the invention may comprise **consistency agents**, preferably a mixture of consistency agents. Suitable consistency agents include e.g.:

i) **solid alcohols**, having e.g. a C₁₂ to C₂₄ chain, e.g. **cetyl alcohol** and/or **stearyl alcohol**.

Cetyl alcohol and stearyl alcohol may be commercially available e.g. under the trademarks **Lorol^R C16** and **Lorol^R C18**, respectively, from Henkel, Germany;

ii) **esters of fatty acid and fatty alcohols**. They may include esterified compounds of fatty acid having e.g. a C₁₂ to C₂₄ chain, saturated or unsaturated, and primary alcohol having e.g. a C₁₂ to C₂₄ chain, e.g. **cetyl palmitate** as commercially available under the trademark **Cutina^R CP** from Henkel, Germany;

iii) **glycerine monostearate** known and commercially available under the trademark

Imwitor^R (Fiedler, loc. cit., p. 906-907; Handbook of Pharmaceutical Excipients, loc. cit., page 225), particularly Imwitor^R 960;

iv) **solid fatty acids**, having e.g. a C₁₂ to C₂₄ chain, e.g. stearic acid and its salts, e.g. aluminium stearate or magnesium stearate;

v) **solid waxes**, e.g. bees wax or carnauba wax; and

vi) mixtures of any of components i) to v).

Consistency agents are preferably present in an amount of from about 1 to about 30 %, e.g. from about 4 to about 10 % by weight based on the total weight of the composition.

If desired, the compositions of the invention may comprise **gelling agents**. Suitable gelling agents include carbomers, e.g. crosslinked poly(acrylic acid) polymers such as known and commercially available under the trademark Carbopol^R (Fiedler, loc. cit., p. 367-372; Handbook of Pharmaceutical Excipients, loc. cit., page 79). Carbopol^R 974P and Carbopol^R 1342 are preferred. The gelling agents are preferably present in an amount of from about 0.2 to about 2 %, more preferably less than about 1 % by weight based on the total weight of the composition.

The compositions of the invention may further comprise **preserving agents**, e.g. microorganism growth inhibitors such as methyl- or propylparabene, phenyl alcohol, **benzyl alcohol**, **propylene glycol**, sorbic acid, and chlorocresol as appropriate. Preserving agents are preferably present in an amount of from about 0.05 to about 1 % by weight based on the total weight of the composition.

The compositions may further comprise **antioxidants** such as butyl-hydroxytoluene, ascorbyl palmitate, sodium pyrosulfite, butyl-hydroxy anisole, propyl p-hydroxybenzoate, methyl p-hydroxybenzoate and tocopherol, as appropriate. Antioxidants are preferably present in an amount of from about 0.01 to about 2.5 % by weight based on the total weight of the composition.

If desired, **pH modifying agents** may be included to bring the pH of the composition to e.g. between about 4 and 6, or by adding a pharmaceutically acceptable buffer system, or by addition of solution (10 %) of sodium hydroxide. A pH of between 4 and 6 is desirable to avoid skin and mucous membrane irritation.

It will be appreciated that although the excipients have been described above by reference to a particular function, any particular excipient may have alternative or multiple functions, e.g. propylene glycol may act as e.g. hydrophilic component and/or preserving agent.

The compositions of the invention may be prepared in conventional manner by dissolving the appropriate amount of lavendustin in the lipophilic components such as lipophilic carrier and consistency agent at elevated temperature, e.g. at from about 60 to about 80 °C, and adding the aqueous phase under stirring and homogenization. Further hydrophilic excipients like buffering agents, gelling agents and preservatives are preferably added to the water phase. Emulsifiers may be added either to the lipophilic or hydrophilic components depending on their HLB values. After homogenization the resultant composition is cooled to room temperature under stirring.

Accordingly, in another aspect the invention provides a **process** for the preparation of a composition of the invention, comprising dissolving a lavendustin derivative of formula I as defined above, or a pharmaceutically acceptable salt thereof, in emollient and optionally further lipophilic components such as consistency agents, if present, preferably at elevated temperature, e.g. at from about 60 to about 80 °C, and adding the water phase, if present, under stirring and homogenization.

The compositions of the invention are indicated for use in the known indications of lavendustin, particularly in the treatment of hyperproliferative disorders such as actinic keratosis, anogenital warts and seborrheic keratosis, and skin cancer.

Therefore, in a further aspect the invention provides a composition of the invention **for use in the treatment of hyperproliferative disorders** such as actinic keratosis, anogenital warts and seborrheic keratosis, and skin cancer.

In another aspect the invention provides a **method for treating hyperproliferative disorders** such as actinic keratosis, anogenital warts and seborrheic keratosis, and skin cancer comprising administering a composition of the invention to the skin or mucous membrane of a patient in need thereof.

In yet another aspect the invention provides the **use of a composition of the invention in the preparation of a medicament** for the treatment of hyperproliferative disorders such as actinic keratosis, anogenital warts and seborrheic keratosis, and skin cancer.

The utility of the compositions of the invention may be observed in standard clinical tests.

A representative clinical trial may be carried out as follows:

A randomised single-centre, double-blind, within-subject vehicle-controlled study of a composition of the invention at a dose of 0.1 to 2 % active agent by weight based on the total weight of the composition over e.g. 10 cm², corresponding to a dose of about 0.1 to 1 mg/cm², is performed in subjects with actinic keratosis, anogenital warts and/or seborrheic keratosis, and/or skin cancer. In total 15 to 36 subjects are treated with the composition once or twice daily for up to two weeks. The therapeutic effect on erythema, edema, pruritus, burning/stinging/pain, and erosion is evaluated separately for each treated lesion. Local tolerability and cosmetic outcome of each treatment and routine safety parameters, including hematology and blood chemistry, are assessed. The compositions of the invention are found to be effective.

The exact amount of lavendustin and composition to be administered depends on several factors, for example the desired duration of treatment and the rate of release of the active agent. Satisfactory results are obtained in larger subjects, e.g. humans, with local application over the area to be treated of a 0.01 to 10 % by weight concentration based on the total weight of the composition, e.g. 0.05 to 3%, preferably 0.1 to 2%, more preferably 0.2 to 1%, most preferably

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about 0.8%, of the lavendustin once or several times a day (for example 1 to 5 times a day). In general, the compositions may be applied to areas of skin and mucous membranes as small as 1 cm² to as large as 1 m². Suitable skin and mucous membrane loadings fall within the range of 0.1 mg/cm² to 10 mg/cm², e.g. 2 mg/cm², of lavendustin composition.

The following Examples illustrate the invention. The following abbreviations are used:

Ex. = Example No.

v = volume

The formulations of Examples 1 to 9 show good physico-chemical stability, and are mild to moderate irritants as determined in vitro using a human epidermis model, and also in a clinical study (see Example 11).

In Examples 1 to 9 compound A may be replaced with compound B or compound C.

Example 10: In vitro penetration

In vitro penetration of compound A of Examples 1 to 4 into human skin was good; concentration of compound A found after 8 hours in the epidermis was between 0.4 and 1.3 $\mu\text{g}/\text{cm}^2$ (calf serum / PBS 1:2 v/v; pH = 7.4).

Example 11: Clinical study

In total 36 subjects with actinic keratosis were treated once or twice daily over up to two weeks with the composition of Example 4. The formulation of Example 4 was effective. Local tolerability and cosmetic outcome were good. Adverse events were minor. Plasma levels of compound A were low, ranging from 0.034 to 3.3 ng/ml.